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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,282	04/05/2001	Andreas Martinus Maria Miltenburg	0/98394US	4006

7590 05/03/2004

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,282	MILTENBURG ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,6,10,12 and 16-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4, 6, 10, 12, and 16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 4, 6, 10, 12, and 16-19 are pending.

2. In view of the amendment filed 2/25/04, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 4, 6, 10, 12 and 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of treating inflammatory rheumatoid arthritis by inhibiting *the proliferation of autoresponsive T lymphocytes* and inflammation associated with rheumatoid arthritis, comprising the step of administering a pharmaceutical composition nasally comprising an effective amount of HC gp-39 or fragment thereof wherein the fragments consist of amino acid sequence selected from one or more SEQ ID NO: 1-8 and a pharmaceutically acceptable carrier, **does not** reasonably provide enablement for a method of treating all autoimmune disease (claim 10), autoimmune disease such as rheumatoid arthritis (4 and 10) by inhibiting the reactivity of lymphocytes associated with said autoimmne disease or the reactivity of lymphocytes that are reactive to all antigens other than HC gp-39 (claim 10) comprising the step of administering a pharmaceutical composition comprising an effective amount of HC gp-39 or fragments thereof wherein said fragments are selected from one or more of SEQ ID NO: 1-8 and a pharmaceutically acceptable carrier, wherein said lymphocytes are reactive to *any* "antigens other than HC gp-39". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of treating inflammatory rheumatoid arthritis by nasal induction tolerance comprising the step of administering a pharmaceutical composition comprising an effective amount of bovine collagen type II HC gp39 (page 10) and a pharmaceutically acceptable carrier (page 14). The specification further discloses HC gp-39 induces the proliferation of PBMC in vitro obtained from some patient with rheumatoid arthritis (See page 15). The specification on page 8 further discloses that administering high or low doses of the tolerogen can attain tolerance or peptides and the amount of tolerogen or peptide will depend on the route of administration, the time or administration, the age or the patients as well as general health conditions and diet.

The specification does not teach how to treat *all* "autoimmune disease" such as osteoarthritis, alcohol-induced liver fibrosis, inflammatory bowel disease, and systemic lupus erythematosus (SLE) and rheumatoid arthritis by "modulating the reactivity of lymphocytes associated with any "autoimmune disease". Given the indefinite number of autoimmune disease, there is insufficient in vivo working example demonstrating that administering HC gp-39 and fragment thereof is effective for treating all autoimmune disease. The specification merely discloses administering HC gp-39 to collagen induced Balb/c mice as a model of rheumatoid arthritis. It is not clear that the reliance of collagen-induced arthritis model accurately reflects the efficacy of treating *all* autoimmune disease in the absence of sufficient guidance and in vivo working examples.

Van Noort *et al*, of record, teach autoimmune diseases can be species and model-dependent (See entire document, pages 167-168, in particular). Given the indefinite number of undisclosed inflammatory autoimmune disease, it is not clear that the reliance on the limited in vivo experimental model accurately reflects the relative efficacy of the claimed method of tolerance induction regimens in treating all autoimmune disease that are mainly T cell mediated.

Anderton *et al*, of record, teach peptide-based immunotherapy of autoimmunity is unpredictable and peptides that inhibit autoimmune disease such as encephalomyelitis in vitro actively induce disease in vivo (See page 370, column 1, second full paragraph, bridging column 2, first paragraph, in particular). Further, Anderton *et al* further teach that clinical trial was suspended due to hypersensitivity reactions in a significant proportion of patients (See page 370, column 2, second paragraph, in particular).

Verheijden *et al* (PTO 1449) teach tolerance can be attained by the amount of autoantigen administered and the **route** of administration is just as important as the autoantigen such as human cartilage glycoprotein-39 (HC gp-39) itself. Verheijden *et al* teach administering a single injection of HC gp-39 in FIA to female BALB/c mice induces clinical signs of arthritis (page 1121, column 2, in particular) whereas intranasal administration of HC gp-39 before immunization completely abrogated DTH response upon challenge (See page 1122, column 2, last paragraph, in particular).

The Merck manual, of record, does not recognize the use of *any* HC gp-39 fragments thereof for treating *any* inflammatory autoimmune disease such as rheumatoid arthritis (See page 420-421, in particular). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Further, the term "reactivity of lymphocytes" is not sufficient to define the biological activity to which the HC gp-39 and fragments thereof inhibit(s). The specification discloses only the method inhibits T cell proliferation.

With regard to lymphocytes are reactive to all "antigens *other than* HC gp-39" which are present in the same tissue as HC gp-39, the specification discloses only lymphocytes are reactive to HC gp-39, the specification does not teach which antigens other than HC gp-39 are present in the same tissue as HC gp-39.

Myers *et al*, of record, teach autoimmune response to collagen type II in the CIA models is complex, requiring specific major histocompatibility complex (MHC) molecules, collagen type II specific T cell and B cell immune responses and their associated cytokines (See page 1862, in particular). Myers *et al* teach although the use of altered peptides in the treatment of autoimmune disease such as rheumatoid arthritis is receiving considerable attention as the evidence of their efficacy continues to growth in vitro studies as well as in animal models. However, the development of such therapeutics for human diseases relies upon significant knowledge of the autoantigen (See page 1873, second full paragraph, in particular). Given the indefinite number of antigens "other than" HC gp-39, a person of skill in the art could not predict which particular antigens is/are essential and could be used in a therapeutic method of treating any autoimmune disease, much less for treating rheumatoid arthritis. In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients.

As such, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments and the declaration of Andrea van Elsas filed 2/25/04 have been fully considered but are not found persuasive.

Applicants' position is that the claims have been amended. Applicants assert that the evidence indicates that expression of HC gp39 is related to monocyte to macrophage maturation. In contrast to many other monocyte/macrophage markers, its expression is absent in normal monocytes and strongly induced during late stages of human macrophage differentiation. Other cell types that express HC gp-39 include chondrocytes and synovial cells and neutrophils, the latter celltype, like macrophages, being heavily involved in inflammatory processes. As a reflection of the involvement of HC gp-39 producing cells in immune disease conditions, raised Human Cartilage glycoprotein-3g plasma levels have been detected in patients with rheumatoid arthritis, and in patients with other inflammatory conditions like osteoarthritis (OA), systemic lupus erythemathosus (SLE), and inflammatory bowel disease (IBD). The declaration of Andrea van Elsas submits that such conditions include *but not limited to* disease like Graves' disease, primary glomerulonephritis, myasthenia gravis, multiple sclerosis, or diabetes.

However, the scope of the amended claim 16 still encompasses a method of treating all autoimmune disease. The specification does not teach how to treat *all* "autoimmune disease" such as diabetes, alcohol-induced liver fibrosis, inflammatory bowel disease, and systemic lupus erythematosus (SLE) and rheumatoid arthritis. Given the indefinite number of autoimmune disease, there is insufficient in vivo working example demonstrating that the claimed method is effective for treating all autoimmune disease. The specification merely discloses intranasal administration of bovine cartilage HC gp-39 to a mouse using the murine collagen-induced arthritis model for rheumatoid arthritis. It is not clear that the reliance of collagen-induced arthritis model accurately reflects the efficacy of treating *all* autoimmune disease in the absence of sufficient guidance and in vivo working examples.

Further, there is insufficient guidance and in vivo working example as to which "antigens *other than* HC gp-39" (claims 4, 10 and 16) that the lymphocytes reactive to in the claimed

method. Finally, the induction of tolerance depends on the route of administration. It is noted none of the base claims recite the particular route of administration.

5. Claims 4, 6, 10, 12 and 16-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of "reactivity of lymphocytes" (claims 4, 10, and 16) "antigens other than HC gp-39" (claims 4, 10, and 16) and a method of treating all "autoimmune disease" (claim 16).

The specification discloses only a method of treating inflammatory rheumatoid arthritis by nasal induction tolerance comprising the step of administering a pharmaceutical composition comprising an effective amount of bovine collagen type II HC gp39 (page 10) and a pharmaceutically acceptable carrier (page 14). The specification further discloses HC gp-39 induces the *proliferation of PBMC* in vitro obtained from some patient with rheumatoid arthritis (See page 15). The specification on page 8 discloses that administering high or low doses of the tolerogen or peptides can attain immune tolerance; the amount of tolerogen or peptide will depend on the route of administration, the time or administration, the age or the patients as well as general health conditions and diet.

With the exception of the specific method of treating rheumatoid arthritis by administering the specific HC gp-39 or the specific peptide as set forth in SEQ ID NO: 1-8 that inhibits T cell proliferation, there is insufficient written description about the structure associated with function of all "antigens *other than* HC gp-39" without the amino acid sequence that the lymphocytes reacted to in the claimed method. Besides inhibiting T cell proliferation, there is inadequate written description about the "reactivity of lymphocytes" for the claimed method.

Finally, the specification discloses only a method of treating only rheumatoid arthritis using the specific HC gp-39 or the specific peptide thereof. Given the lack of a written description of *any* additional representative species of autoimmune disease for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of autoimmune disease to describe the genus encompassed by the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University*

of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments and the declaration of Andrea van Elsas filed 2/25/04 have been fully considered but are not found persuasive.

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However, the amended claim 16 still recites a method of treating all autoimmune disease.

The specification does not reasonably provide a **written description** of "reactivity of lymphocytes" (claims 4, 10, and 16) "antigens other than HC gp-39" (claims 4, 10, and 16) and a method of treating all "autoimmune disease" (claim 16).

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the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

9. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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